

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/565, 31/58 // (A61K 31/565, 31:565) (A61K 31/58, 31:565)		A1	(11) International Publication Number: WO 99/52533
			(43) International Publication Date: 21 October 1999 (21.10.99)
(21) International Application Number: PCT/GB99/00984 (22) International Filing Date: 29 March 1999 (29.03.99) (30) Priority Data: 9807809.0 9 April 1998 (09.04.98) GB (71) Applicant (for all designated States except US): MULTIMED LIMITED [GB/GB]; 82 Harley Street, London W1N 1AF (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): CARRUTHERS, Malcolm, Euan [GB/GB]; Harmond House, Flat 20, 20 Harley Street, London W1N 1AL (GB). (74) Agent: WAKERLEY, Helen, Rachael; Reddie & Grose, 16 Theobalds Road, London WC1X 8PL (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: COMPOSITIONS COMPRISING ETHISTERONE OR ITS DERIVATIVES			
(57) Abstract Treatment of androgen deficiency using a pharmaceutically effective dose of ethisterone or an ethisterone derivative such as danazol. In particular, androgen deficiency in the aging male, also known as the male climateric andropause or the male menopause, can be treated by ethisterone or ethisterone derivatives. Treatment of hypogonadism using ethisterone or ethisterone derivative in combination with testosterone is also effective.			

This Page Blank (uspto)

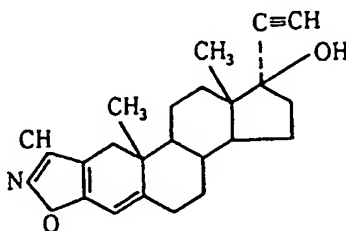
FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

COMPOSITIONS COMPRISING ETHISTERONE OR ITS DERIVATIVES

The present invention relates to the treatment of hypogonadism in men, whether due to an absolute or relative deficiency of testosterone. More specifically, the invention relates to compositions comprising a pharmaceutically effective dose of ethisterone or an ethisterone derivative such as [1,2],oxazolo[4,5-b]-17alpha-pregna-2,4-dien-20-yn-17beta-ol; also known as danazol, Danol, Azol (in Australia) and Danocrine (in the USA).



Androgen Deficiency in the Ageing Male, also referred to as 'The Male Climateric', 'The male menopause' and the 'Andropause' causes a highly characteristic pattern of symptoms which was first recognised nearly sixty years ago (Werner, A. JAMA 112,15,1441-3,1939). As described at that time, the syndrome includes loss of energy, drive and libido, depression, irritability, joint pains and stiffness, and even such typical symptoms of the female menopause as night sweats and hot flushes.

It has been found (Carruthers, M. 'The Male Menopause, Harpercollins', London, 1996) that the symptoms associated with this condition arise due to an absolute or relative

-2-

insufficiency of testosterone, particularly the latter, caused by a reduction in the Free Active Testosterone (FAT); that is a lack of testosterone present in an unbound state in blood plasma. Testosterone in vivo can be bound to sex hormone binding globulin (SHBG) and to a lesser extent, albumin. When bound the testosterone is not freely available to the body or bio-available. One of the best measures of this is the 'Free Androgen Index' (FAI). This is calculated by dividing the Total Testosterone (TT) by the 'Sex Hormone Binding Globulin' (SHBG) and multiplying by a hundred to express it as a percentage. In the healthy, asymptomatic male this is normally in the range 70-100%. Symptoms of the andropause regularly appear when this drops below 50%, except in a few cases where the TT is low and the body appears to compensate by reducing SHBG levels to maintain the FAI.

It has been found that hypogonadism and also the male menopause can be prevented or treated by freeing bound testosterone so that it becomes bioavailable again. Testosterone may be freed, for example, by:

1. decreasing the number of potential binding sites available for testosterone in vivo, for example by reducing the level of SHBG using compounds which antagonise the action of androgens in stimulating SHBG synthesis, and/or
2. introducing an agent which competes for the binding sites, thereby displacing bound testosterone which is returned to systemic circulation.

Pharmaceutical, pharmacological and biological compounds that

-3-

may act effectively include ethisterone and ethisterone derivatives and/or precursors.

One such compound, danazol, is a well established therapeutic agent which has been extensively used in the female for managing a wide range of conditions such as endometriosis, menorrhagia and benign breast conditions such as mastalgia and cystic disorders. Its use in the male is not widely known and has been limited to treatment of enlargement of the male breast (gynaecomastia) and limited research into its use as a male contraceptive. The previous uses of danazol in women and men have all been at relatively high concentrations, for example doses of 200 to 600 mg, and at these concentrations it has been shown that total plasma testosterone is reduced.

It has now been found that using danazol in the male at dose level reduced from that at which it would be conventionally used, for example at a daily dose of not more than 100 mg, re-introduction of testosterone to the systemic circulation in the form of Free Active Testosterone is remarkably effective; that is the FAT is increased leading to a highly effective treatment of the symptoms associated with hypogonadism and with the male menopause.

Danazol is effective, non-hepatotoxic, and does not have intrinsic androgenic, oestrogenic or progestogenic actions. It is an ideal agent for displacing and hence activating testosterone as it has a high affinity for androgen receptors, low affinity for progesterone receptors, and does not interact with oestrogen receptors to any significant extent.

-4-

The importance of only giving low doses of danazol, for example not more than 50 -100mg daily, to men being treated for hypogonadism is because at this low dose, as shown by the clinical studies described later in this application, there is direct suppression of SHBG synthesis by the liver, with a corresponding increase in FAI, apparently without reduction of endogenous total testosterone production.

According to the present invention, ethisterone or an ethisterone derivative is used in the manufacture of a medicament for the treatment of hypogonadism in the male.

The medicament may be for treatment of hypogonadism resulting from any biological or physical cause. In particular, the medicament may be for treatment of any condition where systemic free active testosterone is reduced due to raised levels of SHBG, for example, conditions caused by concurrent/prior treatment with oestrogens, anti-convulsants and/or exposure to xeno-oestrogens.

The medicament may be for treatment of male humans. The medicament may also be a veterinary pharmaceutical preparation for treatment of male animals (such as bulls or rams) where symptoms of hypogonadism are a problem, for example in breeding stock.

Preferably, the ethisterone or an ethisterone derivative is used in the manufacture of a medicament for the treatment of male menopause.

Examples of compounds that fall within the definition of

-5-

"ethisterone derivative" and are suitable in preparation of medicaments according to the invention are :

desogestrel[(17 α)-13-ethyl-11-methylene-18,19-dinorpregn-4-en-2-yn-17-01)];

norethynodrel[(17 α)-17-hydroxy-19-norpregn-5(10)-en-20-yn-3-one];

norgestrel[(17 α)-(±)-13-ethyl-17-hydroxy-18,19-dinorpregn-4-en-20yn-3-one];

norgestrienone[(17 α)-17-hydroxy-19-norpregna-4,9,11-trien-20-yn-3-one];

tibolone[(7 α ,17 α)-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20yn-3-one]; and

norethisterone [(17 α)-17-hydroxy-19-norpregn-4-en-20-yn-3-one] .

Preferably the ethisterone derivative is [1,2],oxazolo[4,5-b]-17alpha-pregna-2,4-dien-20-yn-17beta-ol.

Preferably not more than 100 mg of [1,2],oxazolo[4,5-b]-17alpha-pregna-2,4-dien-20-yn-17beta-ol is used per daily dose in the manufacture of the medicament, preferably the daily dose of [1,2],oxazolo[4,5-b]-17alpha-pregna-2,4-dien-20-yn-17beta-ol is between 25-100 mg. The dose is varied according to body weight, TT and SHBG concentrations.

Danazol may be administered on its own or as an adjunct to other methods of relieving sexual dysfunction problems in men such as libido disorders and impotence, such as applications of alprostadil (Caverject and Medicated Urethral Systems for Erection - MUSE), and drugs which enhance relaxation of the

-6-

corpora cavernosae in the penis, for example those which increase nitric oxide production such as the oral preparation sildenafil (Viagra).

According to the present invention in a further aspect ethisterone, or an ethisterone derivative, together with testosterone is used in the manufacture of a medicament for the treatment of the male menopause.

Preferably the ethisterone or ethisterone precursor used with testosterone is [1,2],oxazolo[4,5-b]-17alpha-pregna-2,4-dien-20-yn-17beta-ol.

Preferably the testosterone is synthetic. It will be appreciated that the action of natural and endogenous testosterone is also enhanced when using the medicament.

Preferably not more than 100 mg of [1,2],oxazolo[4,5-b]-17alpha-pregna-2,4-dien-20-yn-17beta-ol is used with testosterone per daily dose in the manufacture of the medicament, preferably the daily dose of [1,2],oxazolo[4,5-b]-17alpha-pregna-2,4-dien-20-yn-17beta-ol is between 25-100 mg. Preferably, the daily dose of testosterone used in the manufacture of the medicament is in the range of 80-240 mg. The doses of [1,2],oxazolo[4,5-b]-17alpha-pregna-2,4-dien-20-yn-17beta-ol and testosterone are varied according to body weight, TT and SHBG concentrations.

According to a still further aspect of the invention there is provided a pharmaceutically acceptable medicament in a dosage form of 25mg or 50mg or 75mg or 100 mg per day of ethisterone or ethisterone derivative and excipient.

-7-

Preferably the ethisterone derivative is [1,2],oxazolo[4,5-b]-17alpha-pregna-2,4-dien-20-yn-17beta-ol.

Preferably the pharmaceutically acceptable medicament also includes testosterone.

According to a still further aspect of the invention there is provided a pharmaceutically acceptable medicament which includes an ethisterone or ethisterone derivative and testosterone.

Detailed description of the invention

Embodiments of the present invention will now be illustrated with reference to the drawings in which

FIGURE 1 is a chart showing Andropause Check List scores (ACL) on visits to the clinic (visit 1-6) comparing ACL scores for various subjects under dosage regimes of Restandol (TU), Restandol with Danazol (TU+D), Mesterolone (ME), Mesterolone + Danazol (ME + D), Fused Testosterone Crystals (TI) and Fused Testosterone Crystals + Danazol (TI+D);

FIGURE 2 is a chart showing the total sexual activity per month reported by subjects after each visit to the clinic, for the dosage regimes detailed in the description of Fig 1;

FIGURE 3 is a chart showing the concentration of testosterone measured in the subjects at each visit to the clinic, for the dosage regimes described at Fig 1;

-8-

FIGURE 4 is a chart showing the concentration of sex hormone binding globulin (SHBG) measured in the subjects at each visit to the clinic, for the dosage regimes described at Fig 1;

FIGURE 5 is a chart showing the percentage free androgen index (FAI) in subjects at each visit to the clinic, for the dosage regimes described at Fig 1;

FIGURE 6 is a chart showing the concentrations of FSH in the subject at each visit to the clinic, for the dosage regimes described at Fig 1;

FIGURE 7 shows the concentration of luteinizing hormone present in the subjects at each visit to the clinic, for the dosage regimes described at Fig 1;

FIGURE 8 shows the concentration of oestrogen present in the subjects at each visit to the clinic, for the dosage regimes described at Fig 1; and

FIGURE 9 shows the concentration of prostate specific antigen (PSA) present in the subjects at each visit to the clinic, for the dosage regimes described at Fig.1.

[1,2],oxazolo[4,5-b]-17alpha-pregna-2,4-dien-20-yn-17beta-ol, also known as danazol (Danol) is one of a series of heterocyclic steroids distinguished by the presence of an isoxazole group on the A ring of the parent compound ethisterone (17beta-hydroxy-17-alpha-pregn-4-en-20-yn-3one). When administered danazol may, depending on dosage and dose regime, be metabolized to form the following :

-9-

1. Ethisterone (17-hydroxy-17alpha-pregn-4-en-20-yn-3-one)
2. 17-hydroxy-2alpha-(hydroxymethyl)-17alpha-pregn-4-en-20-yn-3-one
3. 17-hydroxy-2-(hydroxymethyl)-17alpha-pregna-1,4-dien-20-yn-3-one
4. 6beta,17-dihydroxy-2alpha-(hydroxymethyl)-17alpha-pregn-4-en-20-yn-3-one
5. 6beta,17-dihydroxy-2alpha-(hydroxymethyl)-17alpha-pregna-1,4-dien-20-yn-3-one.

The dosage level required for the activity is much lower than that used in known dose regimes where danazol is used in the female to treat, for example endometriosis. The preferred dosage is between 25 - 100 mg per day as opposed to 200 to 800 mg per day used previously in different treatments. The dose may be administered orally, nasally, as a solid implant, or intravenously, intramuscularly or transdermally. The active agent may be administered with a suitable carrier or excipient such as lactose (in the case of an orally administered capsule or pill) or as a suspension in an oil such as mannitol. In the case of administration by injection a suitable solvent such as saline solution may be used.

In a preferred embodiment a dose of 50 mg of danazol is administered to the patient daily in the form of a capsule.

In another embodiment the danazol is administered daily in

-10-

combination with a daily dosage of testosterone. The testosterone may be synthetic testosterone. When danazol is administered with testosterone the two may be administered together in a single oral dose, transdermally, by nasal application or by injection or implant, or in two separate doses which may be administered by different dosing methods. For example the combination of methods may comprise an oral dose of danazol in combination with an intra-muscular injection of testosterone. In one embodiment a dose of 50 mg of danazol is administered to the patient daily in combination with a daily dose of testosterone in the range of 80-240mg. In a preferred embodiment a dose of 50 mg of danazol is administered to the patient daily in combination with a daily dose of 160 mg testosterone.

The dose range for testosterone varies with the preparation used and the route of administration. For example, the different dosages of three currently used preparations, testosterone undecanoate (Restandol), mesterolone (Pro-Viron) and implants of pure crystalline testosterone when applied with and without danazol are described in the clinical study.

Whatever the form of testosterone treatment given, and whatever the route of administration, whether orally, by implantation, by intramuscular or subdermal injection, transdermally or even nasally, in many cases, especially those with elevated SHBG levels, the addition of ethisterone or ethisterone derivative will enhance the clinical effectiveness of the testosterone and reduce the amount of it required. For example, many cases of hypogonadism resistant to oral testosterone treatment which would previously have required pellet implantation to get a

-11-

satisfactory clinical effect, respond to the oral treatment plus danazol, and at a lower testosterone dosage level. Furthermore it prolongs the duration of action of testosterone treatments, extending the 'therapeutic window' for free, active testosterone, and making oral doses twice daily as effective as those given three times a day in isolation. It has also been observed to prolong the period of efficacy of both injected and implanted testosterone preparations. This enables reduced dosage to be given with the same duration of action, or the same dosage with an extended duration of action. Because testosterone preparations tend to be expensive, this also has financial implications in reducing the cost of treatment.

It may be that because of the lower doses of testosterone required, or because of its intrinsic pharmacological effects, danazol can reduce the conversion of testosterone to oestrogens. This effect is most marked when high dosages of testosterone given orally as with testosterone undecanoate (Restandol), intramuscularly as with testosterone enanthate, or by pellet implant.

In the following examples the following abbreviations are used:

ACL - Andropause CheckList Score - A questionnaire rating the incidence and severity of symptoms of the andropause. The greater the checklist score, the more severe are the symptoms.

TT - Total Testosterone in nmol/l (NR 13-35)

SHBG - Sex Hormone Binding Globulin in nmol/l (NR 20-45)

-12-

FAI - Free Androgen Index (NR 70-100%)

FSH - Follicle Stimulating Hormone in IU/l (NR 1-6)

LH - Luteinising Hormone in IU/l (NR 0.7-6)

E2 - Oestradiol in pmol/l (NR 55-165)

PSA - Total Prostate Specific Antigen in ug/l (NR < 4.0)

R2,R3,R4,R6 - 2,3,4 or 6 40mg capsules of testosterone undecanoate (Restandol) orally, daily in divided doses.

P2,P3,P4,P6 - 2,3,4 or 6 25mg tablets of mesterolone (Pro-viron) orally, daily in divided doses.

TI - 6-10X200mg of testosterone implants given into the gluteal region at 6monthly intervals.

D0.5, D1 - danazol (Danol) 100mg orally alternate days or daily, respectively.

NR is normal range in a healthy subject.

EXAMPLE 1

A 69 year old man presented complaining of erection problems for 3 years, aches and pains in his hands and feet, and dry skin on his hands, giving an ACL of 8. His TT was normal at 27.4, but his SHBG was raised at 73, giving an FAI of 38%. The diagnosis of hypogonadism was confirmed by raised LH of 6.1 and an FSH of 11.7.

-13-

On this basis, he was started on R3, and at monthly intervals this was increased to R4 and then R6 with only partial relief of symptoms. This was reflected in a lowering of his TT to 21.4, which even with Restandol alone produced reduction of SHBG to 47, gave an FAI of 46, with an LH of 6.7 and FSH of 8.9, and raised E2 of 178.

He was therefore put on TI, and his erection problems rapidly improved. A year later his TT was 35.6, his SHBG had risen to 74, with an FAI of 48%, and total suppression of FSH and LH. However, 3 years after starting treatment his symptoms reappeared, and it was decided to add D0.5 and then D1, which reduced his ACL to 3. Endocrinology after 6 months showed a TT of 21, SHBG 32, FAI 66, LH and FSH <0.5, and E2 111. This ACL and endocrine profile, with an SHBG less than half its original level, and normal PSA, biochemistry and haematology has continued for a further 3 years on TI + D1.

EXAMPLE 2

A forty-four year old man presented with fatigue for 4 years, and erection problems and reduced libido for 2 years. These symptoms, together with dry skin, sweating and hot flushes gave an ACL of 25. A right undescended testis had been removed 32 years previously, being the most likely cause for an early onset of hypogonadism. Endocrinology showed a low TT of 9.2, high SHBG of 64, giving an FAI of 14%, with raised FSH and LH.

Because of a poor clinical response to either P4 or R4, he was given I2, which relieved his symptoms, but became infected on

-14-

several occasions, with extrusion of pellets.

It was therefore decided to revert to oral treatment with P2, which with the addition of D0.5 became fully effective and gave an ACL of 4, with TT of 15.1, SHBG of 20.2 and FAI of 75%. This highly satisfactory clinical situation has been maintained now for 2 years, with normal PSA, biochemistry and haematology.

EXAMPLE 3

A 57 year old man presented with a 3 year history of severe stress followed by fatigue, reduced libido, night sweats, and aches and pains. He had a vasectomy 1 year previously which is a contributory factor to andropause in 20-40% of cases. His ACL was 10, with a TT of 20, SHBG 56.7, FAI 35, FSH 10.2 and E2 <20. As he needed R6 to control his symptoms, and after 3 months on this his TT was 22.2 but his SHBG had risen to 112, giving an FAI of 19.8, it was decided to try TI. After 6 months, his TT was 30.6, SHBG remained very high at 95.3, giving an FAI of 32%. During the following 2 years with TI alone, the SHBG's were 82.1, 85, 54, and 81. It was therefor decided to add D0.5 to the 6 monthly implant regime, and the SHBG's fell to 35, 34, and 24. This gave optimal clinical results, with high FAI's and no abnormalities of PSA, biochemistry or haematology.

EXAMPLE 4

The 43 year old patient was complaining of fatigue for 5 years, and reduced libido and erection problems for 2 years, with an ACL of 34. He gave a history of removal of a left sided varicoele, followed by severe scrotal swelling, 7 years ago, and non-specific urethritis which is a common contributory factor

-15-

to hypogonadism, 22 years ago. His TT was 14, and SHBG 66, giving an FAI of 21%, FSH 6.9, LH 6.6 and E2 84.

With this diagnosis of hypogonadism, largely due to a raised SHBG, he was started on P4 + D0.5. At 3 months, his symptoms were largely relieved, the ACL having been reduced to 9, and his libido and erections had improved with daily or twice daily intercourse and reported stupendous orgasms. The TT was 31, SHBG 27, FAI 115%, FSH 5.1, LH 1.6 and E2 73.

The patient has remained relatively asymptomatic, with ACL's under 7 for the last two years, SHBG's of 18, 23, 24, and 22, PSA's, full biochemistry and haematology profiles staying normal.

EXAMPLE 5

A 42 year old man complained of fatigue, depression, aches and pains in the hands and feet, hot flushes, a feeling of premature ageing, reduced libido and erection problems for 2 years, giving an ACL of 26. He gave a history of having had mumps 10 years before, and stress from his marriage. Surprisingly his TT was raised at 50, but with an SHBG of 72, giving an FAI of 69.4. The FSH was 5.9, LH 6.0 and E2 120.

Because of the characteristic clinical picture of the andropause, it was decided to treat him with D1 alone. Within 3 months his sexual activity had increased from once a month to twice a week, and his ACL had reduced to 14. His testosterone had remained high at 48, the SHBG was down to 39, giving a FAI 123%, with an FSH of 4.5, LH 2.9, and E2<44. The clinical

-16-

response has been maintained for 2 years with SHBG's of 17, 19 and 23, again with no adverse effects on PSA, the full biochemistry or haematological profile.

EXAMPLE 6

A patient aged 51 presented with lethargy and depression for 4 years, reduced libido for 3 years, night sweats for 1 year, and an ACL of 39. The TT was 17, SHBG 58, FAI 29%, FSH 2.8, LH 2.2, and E2<37.

On R6+ D1 at 3 months his symptoms had decreased somewhat, his ACL being 25. His TT was 58, which with an SHBG of 20 gave an FAI of 290%, the FSH being 1.0, LH 0.7 and E2 117. This appeared excessive, and so he was changed to R4+D1, and 6 months after starting treatment he had been able to come off antidepressants, and his ACL was 21. Most unusually, on R4, which is an average dose, combined with D1, TT have remained well above the usual levels achieved, at 46, 64 and 50, with corresponding SHBG's of 23, 23 and 20, giving FAI's of 200, 278, and 250 at the 6 monthly follow-up visits. The clinical results of a further reduction of testosterone dosage to the lowest level of R2, following the principle of restoring the endocrinology to as normal a pattern as possible and using the smallest doses of hormones which will achieve this, so far seem to be excellent.

EXAMPLE 7

The 51 year old patient was complaining of reduced libido and depression for 5 years, with night sweats for 3 years and an ACL of 19. The TT was 18, SHBG 52, FAI 35% FSH 5.2, LH 4.6 and

-17-

E2 79. After 3 months on R4+ D1, his ACL had fallen to 8, sexual activity had doubled, and his TT was 41, SHBG 15, FAI 273%, FSH 1.0, LH <0.5 with an E2 of 62. Reducing to R2+D1, the clinical benefits were fully maintained, the endocrine results 6 months later being TT 19, SHBG 15, FAI 127%, FSH 1.9, LH 0.9, and E2 40. One year later, they were TT 20, SHBG 20, FAI 100%, FSH 2.3, LH 1.2 and E2 44.

CLINICAL TRIAL

The following is included by way of further exemplification of the use of the medicament according to the invention.

One thousand men aged 31-80 (mean age 54), were seen in a private clinic, the Gold Cross Medical Centre, complaining of a range of symptoms which to them or their GP indicated the "male menopause" or andropause. These consecutive referrals were evaluated at interview by administering a questionnaire, the "Andropause Check List" which rated each symptom on a five point rating scale as being absent(0), slight(1), moderate(2), severe(3) or total(4). It also included questions on the monthly frequency of intercourse and masturbation. A detailed history was taken focussing especially on factors which might affect testicular function and this was entered onto a computerised database (Microsoft Access).

An extensive clinical examination was also carried out, particularly to look for signs of endocrine imbalance such as gynaecomastia or altered hair distribution, as well as alterations in the penis, testes, scrotum and prostate, including scrotal and transrectal ultrasound where necessary.

Fasting blood samples were taken between 9 and 12 am to

-18-

minimize the effects of diurnal variation, and analyses included the standard full biochemical, lipid and haematology profiles, prostate specific antigen and routine urine analysis. The endocrine assessment included follicle stimulating hormone (FSH) and luteinizing hormone (LH) prolactin, total testosterone (TT), dihydrotestosterone (DHT), sex hormone binding globulin (SHBG), oestradiol (E2) cortisol and either total thyroxine or TSH.

In addition to any medication, patients received advice on general measures such as relaxation, reduction of alcohol intake, weight loss and exercise in accordance with the findings on their lifestyle profiles. They were then treated with either testosterone undecanoate (TU - Restandol) 40-80mg bd (twice daily) or tds (three times daily), or mesterolone (ME - Pro-Viron) 25-50 mg bd or tds, the dosage being adjusted according to clinical response. Implantation of 6-10 200mg pellets of fused testosterone crystals (TI - Organon) into alternate buttocks at 6 monthly intervals was used as the method of choice in some cases who found oral treatment either ineffective or inconvenient.

As a supplement to any of the above treatments, over the last four years of the study, Danazol (D - Danol - Sanofi Winthrop) 100mg alt mane (dose taken alternate mornings), or depending on the response, mane daily (dose taken each morning), was added to the androgen regime, particularly in cases with a raised SHBG, and those who did not respond to any of the testosterone treatments alone.

During treatment, the severity of symptoms and level of sexual activity on the Andropause Check List score was reassessed at three monthly intervals, as well as weight, blood pressure, resting pulse rate, full endocrine, biochemical and

haematological profiles, and in some cases ultrasound studies of the prostate and testes. In all cases, subjects were used as their own controls in the comparison of the effects of treatment. All results were stored in a specially designed Microsoft Access database, and stabilised analyses were carried out using the SPSS version 9 programme.

Results

The results of 480 men given TU, 129 given TU+D, 141 given ME, 36 given ME+D, 118 given TI and 10 given TI+D were analysed for up to six 3-6 monthly visits i.e. up to 3 years, visit 1 representing the paired pre-treatment findings for the same individuals in each case i.e. using each man as his own control.

The severity of the symptoms as assessed by the total Andropause Check List (ACL) score fell equally in those cases when Danazol (Danol) had to be added, even though many of these cases had previously been resistant to treatment (Fig.1)

Sexual activity in terms of intercourse per month increased equally in cases given Danazol (Danol) who had failed to respond to any of the previous treatments (Fig.2). Activity was highest in the T1 and D groups.

Particularly with Testosterone Undecanoate (TU) and Mesterolone (ME), the addition of Danazol (Danol) appeared to raise the total testosterone levels recorded at the follow-up visits to a statistically significant degree (Fig.3).

The most marked change observed when Danazol (Danol) was added to the treatment regime was in the reduction of Sex Hormone Binding Globulin, which started above the normal range (20-45nmol/l) in all three groups where Danazol needed to be given,

-20-

and uniformly ended at the bottom end of it. Those who required testosterone implants and Danazol (Danol) to obtain a satisfactory clinical response, were observed to have had initially much the highest SHBG levels. Of the three forms of testosterone, only Restandol produced any reduction in SHBG levels on its own (Fig.4).

The addition of Danazol (Danol) to the three testosterone treatments markedly increased the Free Androgen Indices obtained, in the case of the two oral treatments to nominally in excess of 100% in some cases (Fig.5).

The effect was almost certainly also present in the implant group, probably to an even greater extent. However it could not be demonstrated in this study because the blood samples were taken at the end of the six month treatment period when the total testosterone levels had fallen back to almost pre-treatment levels as seen in Fig. 3, and symptoms of hypogonadism were beginning to return. In a previous study, samples had been taken 3 months after implantation, and showed mean testosterone levels of 45nmol/l, which together with the reduced SHBG obtained by Danazol (Danol) treatment would have given an FAI in excess of 100% for most of the six month period.

The pre-treatment FAI's in the groups requiring Danol were lower in all three groups before treatment (Visit 1).

Both the gonadotrophins, particularly the FSH, showed greater reductions when Danazol (Danol) was added to the testosterone treatment, probably because of the feedback inhibition of the hypothalamic GnRH due to the much higher FAI's (Figs 6 and 7).

There appeared to be no significant change in oestradiol levels

-21-

with treatment, (Fig.8) other than possible increase in the TI and D group due to increased aromatisation of the higher total testosterone levels noted previously.

PSA levels did not appear to change significantly with treatment (Fig.9), except for a possible increase in the ME+D group, and decrease in the TI+D group. This may be related to the trebling of DHT with ME alone, with no increase in the TI alone group. These effects are being investigated further in relation to total and free PSA's and the ratio between them.

The addition of danazol (Danol) to three different forms of testosterone treatment for hypogonadal men greatly increased their efficacy, particularly in cases where SHBG levels were raised. The use of this new agent in the field of treatment of andropausal conditions makes it possible for the first time to specifically reverse the rise in SHBG which tends to occur naturally with age, and restore a more youthful endocrine profile, with the attendant clinical benefits.

Other clinical conditions, such as when there is a rise in SHBG and other carrier proteins due to increased oestrogen levels (Carruthers and Hobbs, J. Clin. Path., 17, 2, 117-9, 1969) as seen in hepatic disease, and with drugs such as anticonvulsants (Toone, B.K. et al. J Neurol., Neurosurg. and psych., 46, 824-6, 1983) and with xanooestrogen's make danazol a valuable preparation either on its own or in conjunction with exogenous testosterone.

The usage of danazol, optionally in combination with low dosage testosterone treatment, appears to give for the first time a unique opportunity to adjust the level of TT, SHBG and hence FAI to mimic a normal youthful endocrine pattern even in middle-aged and elderly men. This should give clinical

benefits in both treating hypogonadal men, and in the field of preventive medicine, where maintaining an adequate level of testosterone activity is being shown to be a key factor.

C L A I M S :

1. Use of ethisterone or an ethisterone derivative in the manufacture of a medicament for the treatment of hypogonadism in the male.
- 5 2. Use according to claim 1 where the medicament is for the treatment of male menopause.
3. Use according to claim 1 or 2 where the ethisterone derivative is [1,2],oxazolo[4,5-b]-17alpha-pregna-2,4-dien-20-yn-17beta-ol.
- 10 4. Use of not more than 100 mg of [1,2],oxazolo[4,5-b]-17alpha-pregna-2,4-dien-20-yn-17beta-ol per dose in the manufacture of a medicament for the treatment of the hypogonadism in the male.
5. Use according to claim 4, where the medicament is for the
15 treatment of the male menopause.
6. Use according to claim 4 or 5 where between 25-100mg of [1,2],oxazolo[4,5-b]-17alpha-pregna-2,4-dien-20-yn-17beta-ol is used per dose.
7. Use according to any preceding claim where the dose also
20 includes testosterone.
8. Use according to claim 7 where each dose includes up to 240mg testosterone.
9. A method for the prevention or treatment of hypogonadism in the male, comprising administration of an ethisterone or
25 ethisterone derivative.

10. A method according to claim 9, for treatment or prevention of the male menopause.

11. A method according to claim 9 or 10 wherein the ethisterone derivative is [1,2],oxazolo[4,5-b]-17alpha-pregna-
5 2,4-dien-20-yn-17beta-ol.

12. A method according to claim 9, 10, or 11 further comprising the administration of testosterone.

13. A method of treatment of a medical condition caused by raised levels of Sex Hormone Binding Globulin, comprising
10 administration of an ethisterone or ethisterone derivative.

Fig 1 - ACL Scores

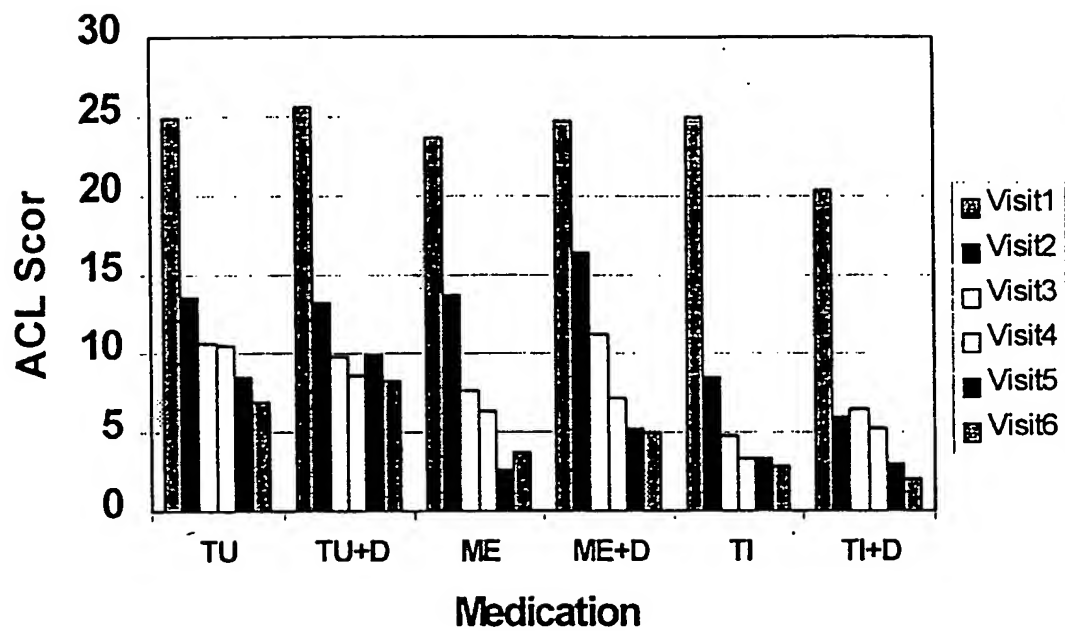


Fig 2 - Sexual Activity

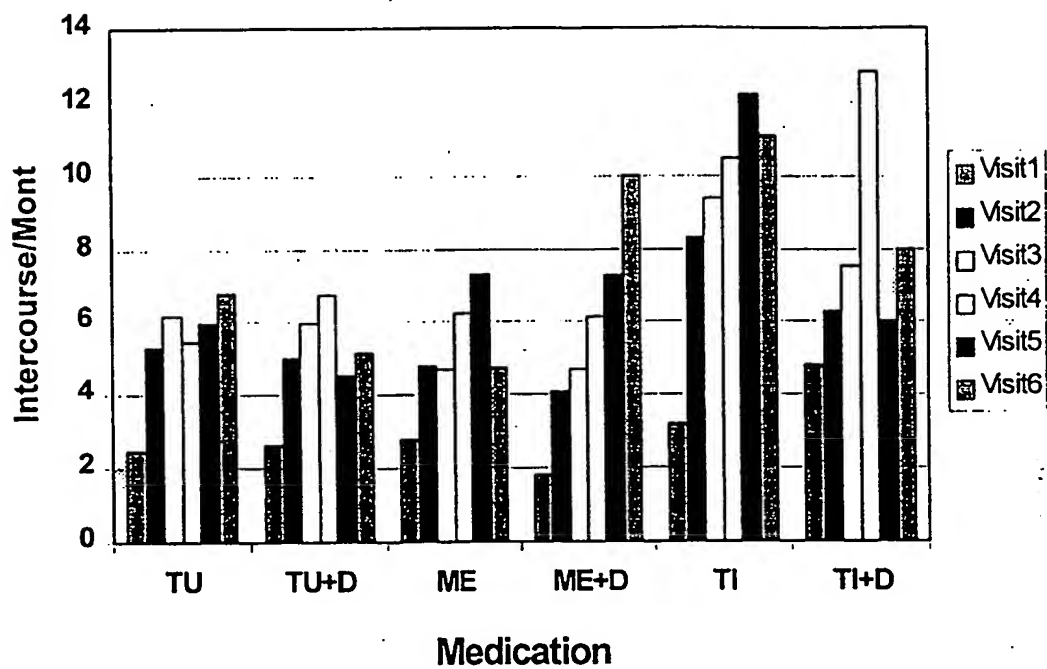
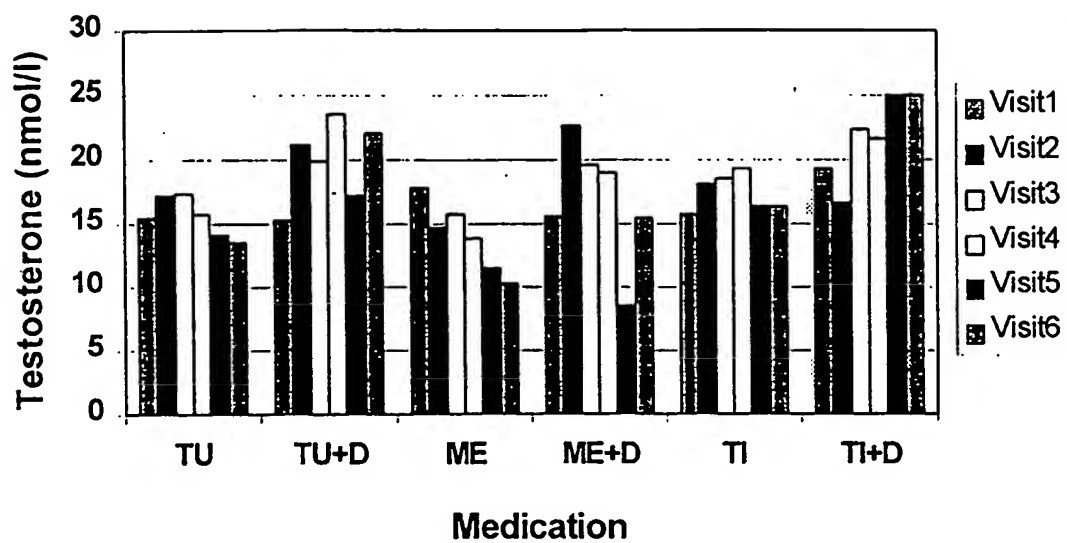


Fig 3 - Total Testosterone

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00984

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/565 A61K31/58
(A61K31/58,31:565)

/(A61K31/565,31:565),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 13800 A (SCHERING AG ;YALLAMPALLI CHANDRA (US); GARFIELD ROBERT E (US)) 26 May 1995 (1995-05-26) page 5, line 24 - page 6, line 8	1,2, 7-10,12
Y	page 9, line 7-10; claims 1,17 ---	1-12
X	WO 97 24148 A (CYGNUS THERAPEUTIC SYSTEMS) 10 July 1997 (1997-07-10) page 3, line 25-28	1,2, 7-10,12
Y	page 12, line 7-26 ---	1-12
Y	EP 0 804 926 A (JENAPHARM GMBH) 5 November 1997 (1997-11-05) the whole document -----	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

12 July 1999

Date of mailing of the international search report

24.09.99

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl
Fax: (+31-70) 340-3016

Authorized officer

Herrera, S

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/ 00984

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 - 12

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-12

Use of ethisterone for the treatment of diseases caused by hypogonadism

2. Claim : 13

Use of ethisterone for the treatment of diseases caused by sex hormone binding globuline

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/00984

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9513800 A	26-05-1995	US 5595970 A	21-01-1997
		AU 8144694 A	06-06-1995
		BR 9408062 A	24-11-1996
		CA 2176727 A	26-05-1995
		CN 1135177 A	06-11-1996
		CZ 9601400 A	11-09-1996
		EP 0730445 A	11-09-1996
		FI 962110 A	15-07-1996
		HU 74459 A	30-12-1996
		JP 9505069 T	20-05-1997
		NO 961994 A	16-07-1996
		NZ 276106 A	27-05-1998
		PL 314466 A	16-09-1996
		SK 63496 A	05-03-1997
-----	-----	-----	-----
WO 9724148 A	10-07-1997	AU 1429697 A	28-07-1997
-----	-----	-----	-----
EP 0804926 A	05-11-1997	DE 19619045 C	13-11-1997
		US 5855905 A	05-01-1999
-----	-----	-----	-----